PATENT

IN THE UNITED STATES Patent and Trademark Office

In re Application of:	)	Confirmation No. 6566
Gregory J. Riggins *et al.*	)	Group Art Unit: 1642
Serial No.: 09/853,880	)	Examiner: C. Yaen
Filed: May 14, 2001	)	
For: FOUR GENETIC TUMOR MARKERS SPECIFIC FOR HUMAN GLIOBLASTOMA	)	Atty. Docket No. 000250.00003

RESPONSE

Commissioner of Patents
c/o Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

In response to the Office Action mailed December 15, 2004, applicants request reconsideration of the patentability of the claimed invention. This filing includes:

- Loging *et al.*, *Genome Research*, Vol. 10, pp. 1393-1402, 2000* (Tab I)
- Kuan *et al.*, "GPNMB: A Molecular Target for Human High-Grade Glioma Immunotherapy" (Tab J)

All claims are rejected as not enabled by the specification. This rejection is respectfully traversed. The Patent and Trademark Office doubts the enablement of the present invention because GPNMB has allegedly not been shown to be a tumor associated antigen. While the Patent and Trademark Office concedes that the GPNMB mRNA is up-regulated in glioblastoma, it doubts the correlation of GPNMB mRNA expression and GPNMB protein expression.

* This publication was discussed in the amendment filed February 9, 2004, but apparently omitted from the filing.

The enclosed manuscripts of Kuan *et al.* demonstrates that GPNMB protein and mRNA expression are indeed correlated. Figure 6 shows the significant correlation between (1) astrocytomas and glioblastomas (brain tumors) that positively stain with anti-GPNMB antibody and (2) the amount of GPNMB mRNA produced by the brain tumors. Figure 7 shows immunohistochemistry in which anti-GPNMB antibodies labeled glioblastoma tissues demonstrating expression of the antigen in the tumor cells. These data demonstrate that GPNMB protein is expressed in brain tumors and that the protein expression correlates with the mRNA expression.

The Patent and Trademark Office cites two references which are said to indicate the unpredictability of anti-tumor antibody therapy in general. First, these two references are 13 and 9 years old. In the space of the intervening decade, much has changed. Many therapeutic antibodies for cancer have been approved and come into regular medical practice.

Gemtuzumab Ozogamicin (Mylotarg™) was approved in 2000 for treating acute myeloid leukemia. This drug is an antibody linked to a chemotherapeutic drug, calicheamicin. Tab A.

Trastuzumab (Herceptin™) is used for treating breast cancer. Approved by the FDA in 1998, it targets the HER2 protein, which is excessively expressed on approximately 30% of metastatic breast tumors. Tab B.

Alemtuzumab (Campath™) is used for treating B-cell chronic lymphocytic leukemia (B-CLL). It is a humanized monoclonal antibody which targets CD52 and stimulates the immune system. Tab C. It was approved by the FDA in 2001.

Bevacizumab (Avastin™) is a monoclonal antibody against VEGF, approved for use in colorectal cancer. Tab D. It was approved by the FDA in 2004.

Rituximab (Rituxan™) is a chimeric antibody directed against CD20. It is used in treating non-Hodgkin's lymphoma. Tab E. It was approved in 1997 by the FDA. Similarly, ibritumomab tiuxetan (Zevalin™) targets CD20 and is used for treating non-Hodgkin's lymphyoma. Tab F.

Cetuximab (Erbitux™) is a monoclonal antibody which targets EGF receptors. Tab G. The FDA approved it in 2004 for treating colorectal cancer.

Tositumomab (Bexxar™) also targets CD20 and is used for treating non-Hodgkin's lymphoma. Tab H. It was approved by the FDA in 2003.

As demonstrated by this long list of approved anti-tumor antibodies, the references cited by the Patent and Trademark Office are simply out of date and do not reflect the current widespread use of antibody therapeutics, particular for treating cancer.

Moreover, the references are cited as raising issues which are merely of a speculative nature. For example, the Curti reference points to several spaces with different physiological characteristics which must be traversed as "potential impediments" to effective drug delivery. Page 30, column 2, line 2. See also page 35, column 1, lines 19-24 ("significant potential physical barriers"). Curti advocates research on these questions in order to improve chemotherapy, gene therapy, and immunotherapy. "It is only when this is understood that the full potential of chemotherapy, gene therapy, and immunotherapy can be realized." Page 36, column 2, lines 10-13. Curti does not teach that any of these factors prevents operability– only that improvements could be made by studying these issues. Thus, Curti does not present a teaching of unpredictability about any particular type of therapy, but rather discusses

theoretically aspects which could be investigated to improve drug delivery. Certainly such a discussion does not render unpredictable the efficacy of all anti-tumor drugs.

The cited Jain reference also discusses a broad range of drugs including monoclonal antibodies, cytokines, antisense oligonucleotides, gene-targeting vectors, and genetically engineered cells. Jain states that "clinical results to date have not met the high expectation extrapolated from carefully planned and performed preclinical studies." Page 1080, column 1, lines 308. Jain advocates new training programs to investigate and educate regarding "biochemical and physiological barriers to successful cancer treatments." Page 1080, column 2, last paragraph. Jain does not demonstrate that any particular type of agent, *e.g.*, antibodies is ineffective, but rather that "molecular medicine" had heretofore been disappointing. As demonstrated above, Jain's advocacy piece was followed by the approval of many antibodies for treatment of cancers. Jain's piece does not raise any particularized reason to think that the present invention would not work.

It is respectfully submitted that the Patent and Trademark Office has not made a *prima facie* case of non-enablement, having relied on old and speculative articles that present no relevant or particularized information about the claimed invention. Instead, the articles discuss anti-cancer treatments in general, which as demonstrated above, have experienced a renaissance in the last decade.

Withdrawal of this rejection is respectfully requested.

Respectfully submitted,

Dated: March 17, 2005

By: 

Sarah A. Kagan
Registration No. 32,141

Banner & Witcoff, Ltd.
Customer No. 22907